Coronary Flow as a Surrogate Endpoint in Phase II Studies of Myocardial Infarction

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Medical therapy for acute myocardial infarction

- *Presentation: patient with chest pain and ST elevation by ECG presents within 6 hours of pain onset*
- *Diagnosis: blockage of coronary artery/myocardial infarction*
- *Treatment: medical therapy to lyse presumed fibrin/platelet clot*

Etiology

- *Plaque rupture in coronary artery*
- *Platelet activation*
- *Thrombin activation*
- *Cross-linking of platelets with fibrinogen*
- *Accumulation of platelet/fibrin mesh blocking coronary artery*

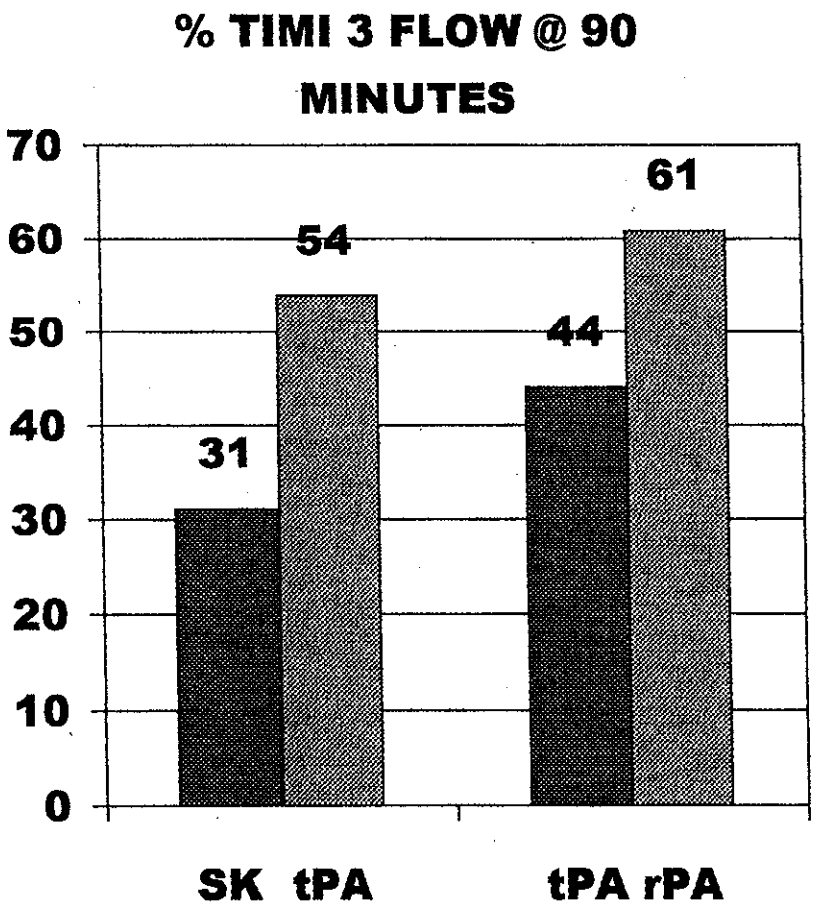
Medical therapy

- *Setting: no invasive intervention planned/available*
- *Fibrinolysis (tPA, streptokinase)*
- *Platelet inhibition (aspirin)*
- *Thrombin inhibition (heparin with tPA)*
- *Objective: reduce mortality by safely reopening arteries*

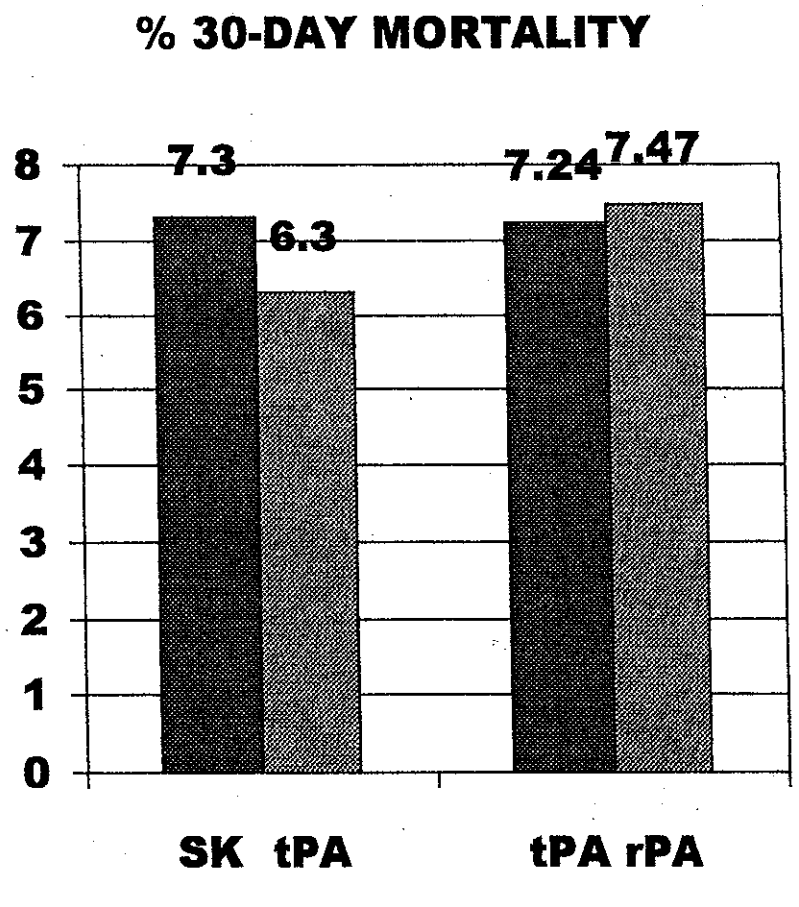
Surrogate in Phase II Studies

- ***Coronary angiography 90 minutes following medical therapy***
- ***Measurement of TIMI flow grade***
  - Grade 3: Complete flow
  - Grade 2: Partial flow
  - Grade 0/1: Low/no flow
- ***Clinical endpoint studies always follow***
- ***Examples: tPA, TNK, rPA, nPA,...***

Flow vs. Mortality



GUSTO-I RAPID-2

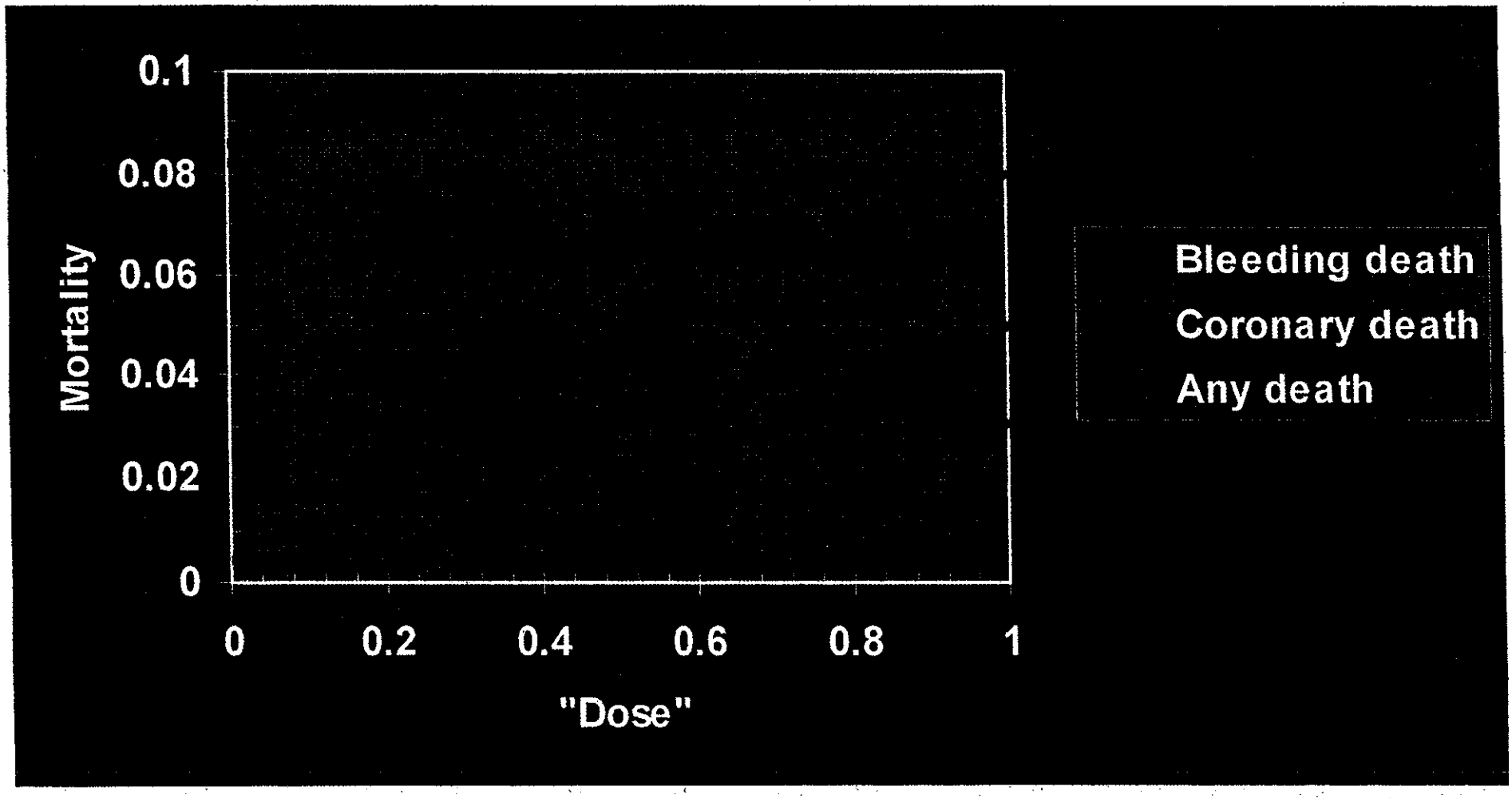


GUSTO-I GUSTO-III

Angiography surrogate

- May be useful in selecting candidate dose regimens
  - Commonly used regimens developed in both GUSTO-I and GUSTO-III
- Does not capture the 'full net effect' of treatment
  - Otherwise, would expect rPA better in GUSTO-III

Why doesn't angiography capture full net effect?



Abciximab Phase III Objectives

- Add *anti-platelet (abciximab)* to reduced-dose fibrinolytic (rPA) and anti-thrombin (heparin) agents to:
  - ↑ Infarct vessel patency (flow)
  - ↓ Reocclusion
  - ↑ Microvascular flow
  - ↓ Intracranial hemorrhage

Hypothesized drug effects

	Coronary Patency	Coronary Reocclusion	Microvascular Flow	Bleeding
Fibrinolytic	+++	+/−	+?	−−
Anti-Platelet	++	+++	++?	−−
Anti-thrombin	+	+	+?	−−

While a fibrinolytic works to open an artery, platelets and thrombin work to re-close it!

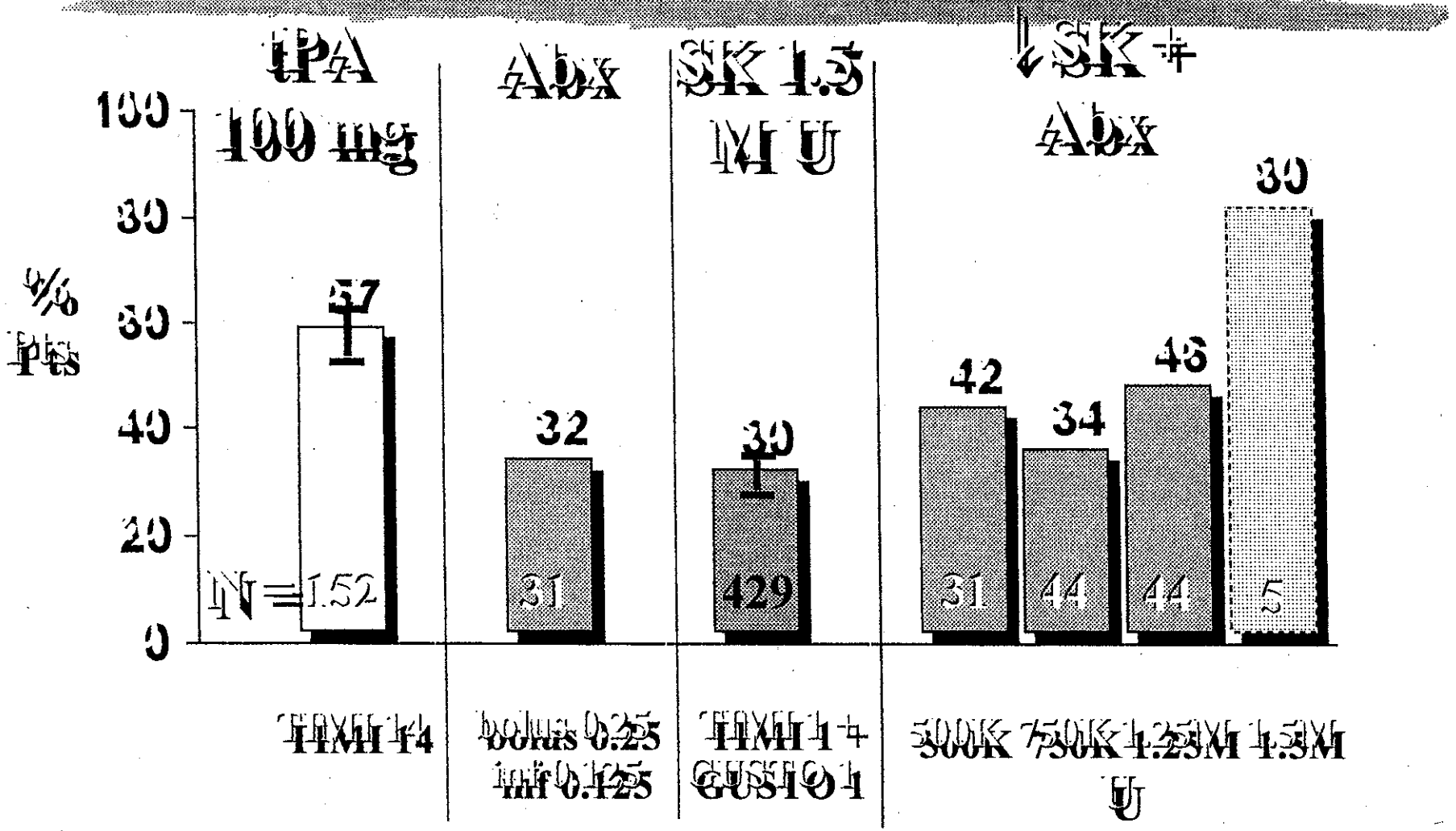
Phase II Dosing Questions: Fibrinolytic+abciximab+heparin

- Fibrinolytic
  - tPA (specific)
  - SK (not specific)
  - rPA (intermediate)
  - None
- Heparin
  - 'Low' dose
  - 'Very low' dose
- Abciximab
  - Bolus
    - 0.25 mg/kg
    - 0.3 mg/kg
  - Infusion: single dose
- Control
  - Standard tPA+heparin
  - Standard rPA+heparin

TIMI 14: Initial Phase Design

- *35 patients per group*
- *Sequential selection of dose groups*
- *Confirmed selected dose*
- *900 patients to evaluate 13 experimental regimens and select 1*
- *Surrogate endpoint required for selecting from many potential dosing strategies*

TIMI 3 FLOW (CORE LAB) AT 90 MINUTES



Angiography Surrogate

- 'Quickly' ruled out two strategies
  - SK tested with multiple doses
  - Abciximab only had much lower success rate
- Although angiography does not capture the full net effect of treatment, we were willing to discontinue study of these treatments

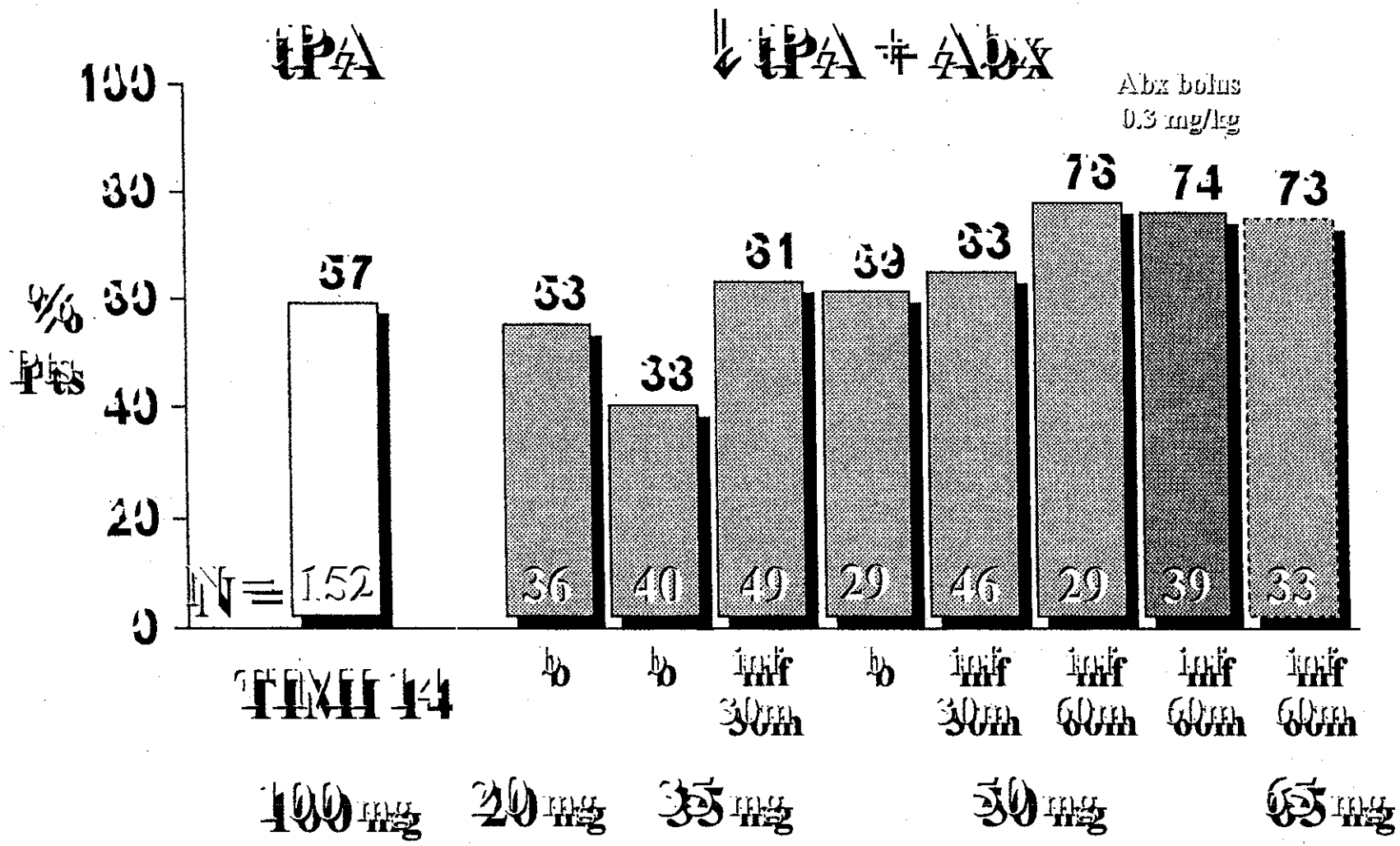
tPA dosing with Abciximab

	20 mg	35 mg	50 mg	65 mg
Bolus	✦	✦	✦	
30 min 15 mg bolus		☼	☾	
60 min 15 mg bolus			☼	☾

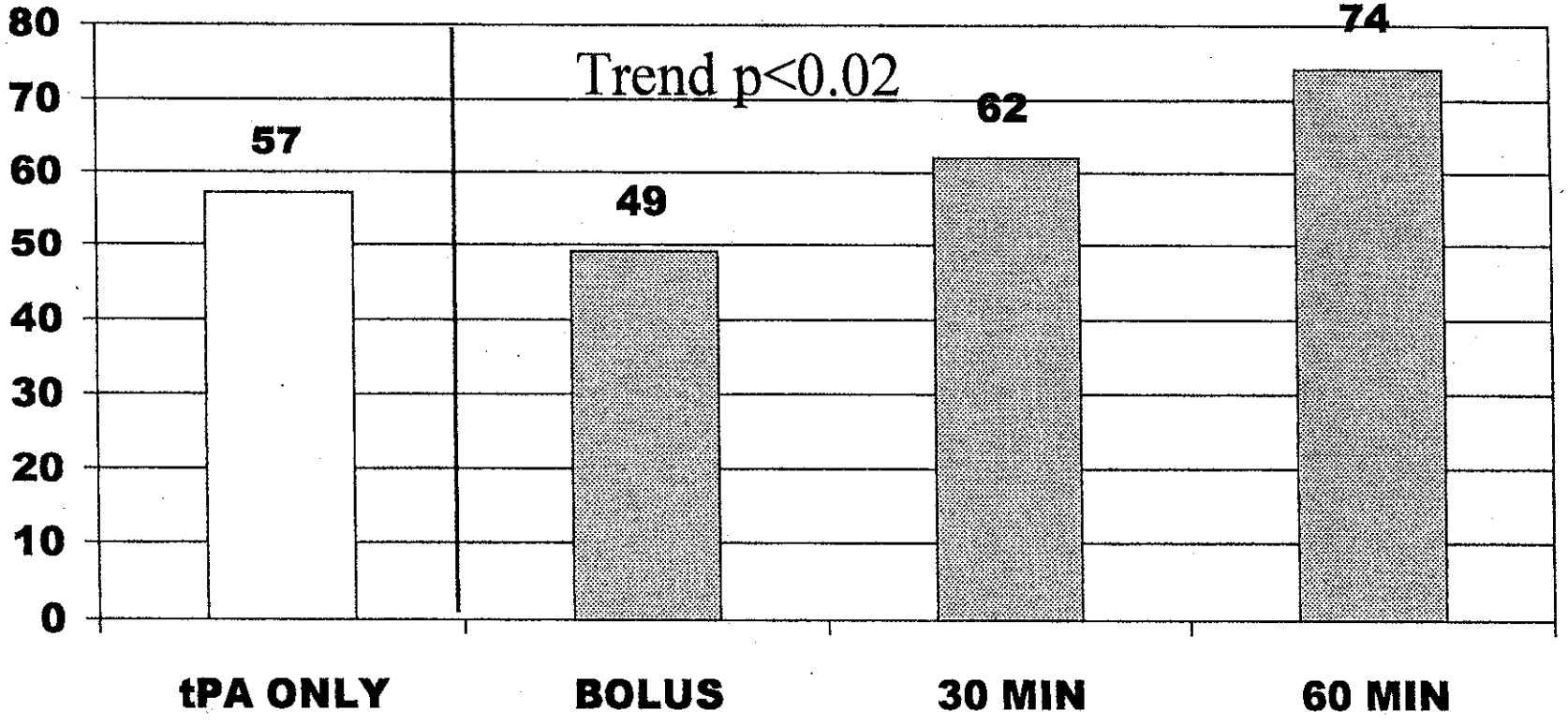
☼ =35-40 mg/hr infusion

☾ =50-70 mg/hr infusion

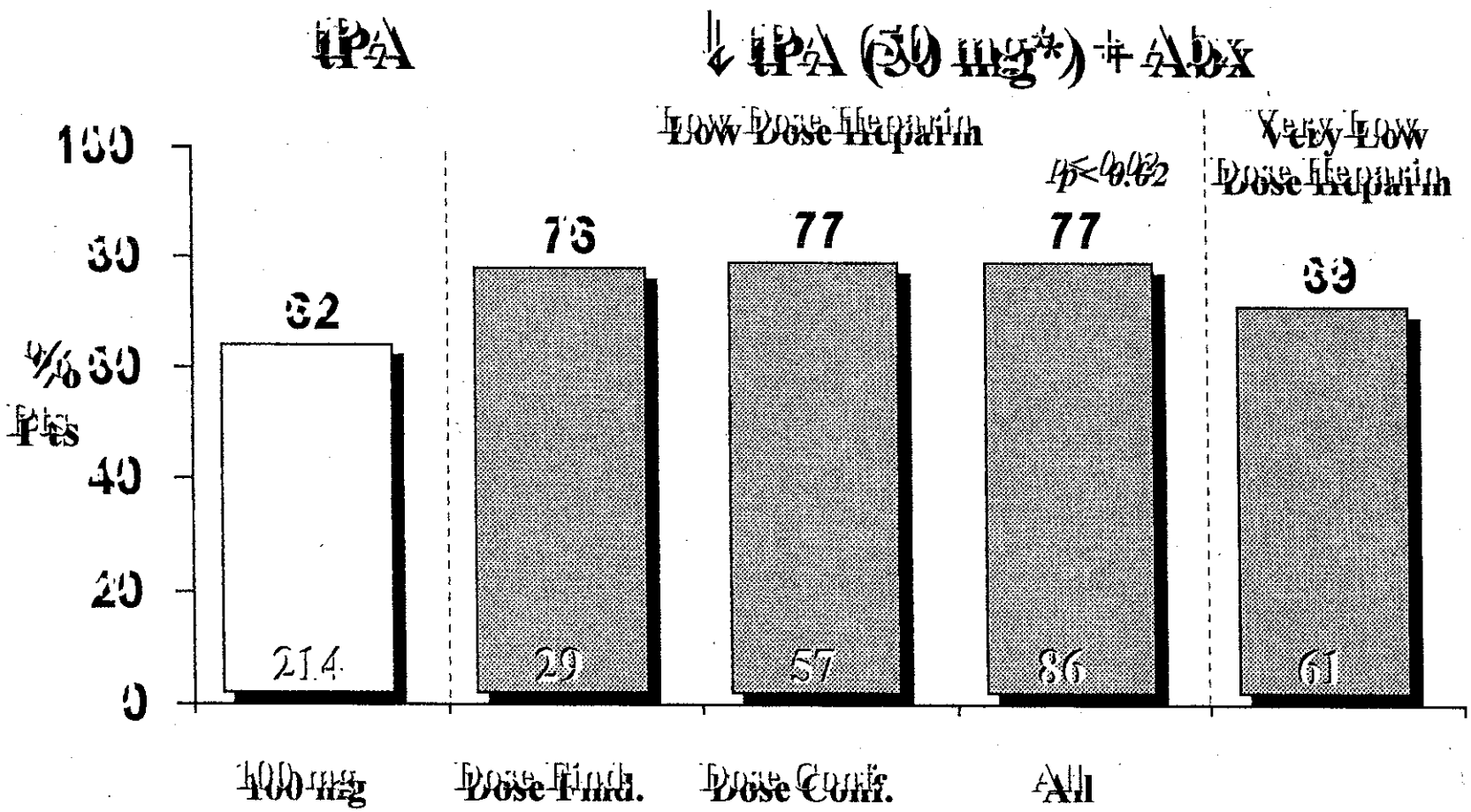
TIMI 3 FLOW AT 90 MINUTES (Dose Finding)



90 MINUTE TIMI 3 FLOW BY DURATION OF tPA (Dose Finding)



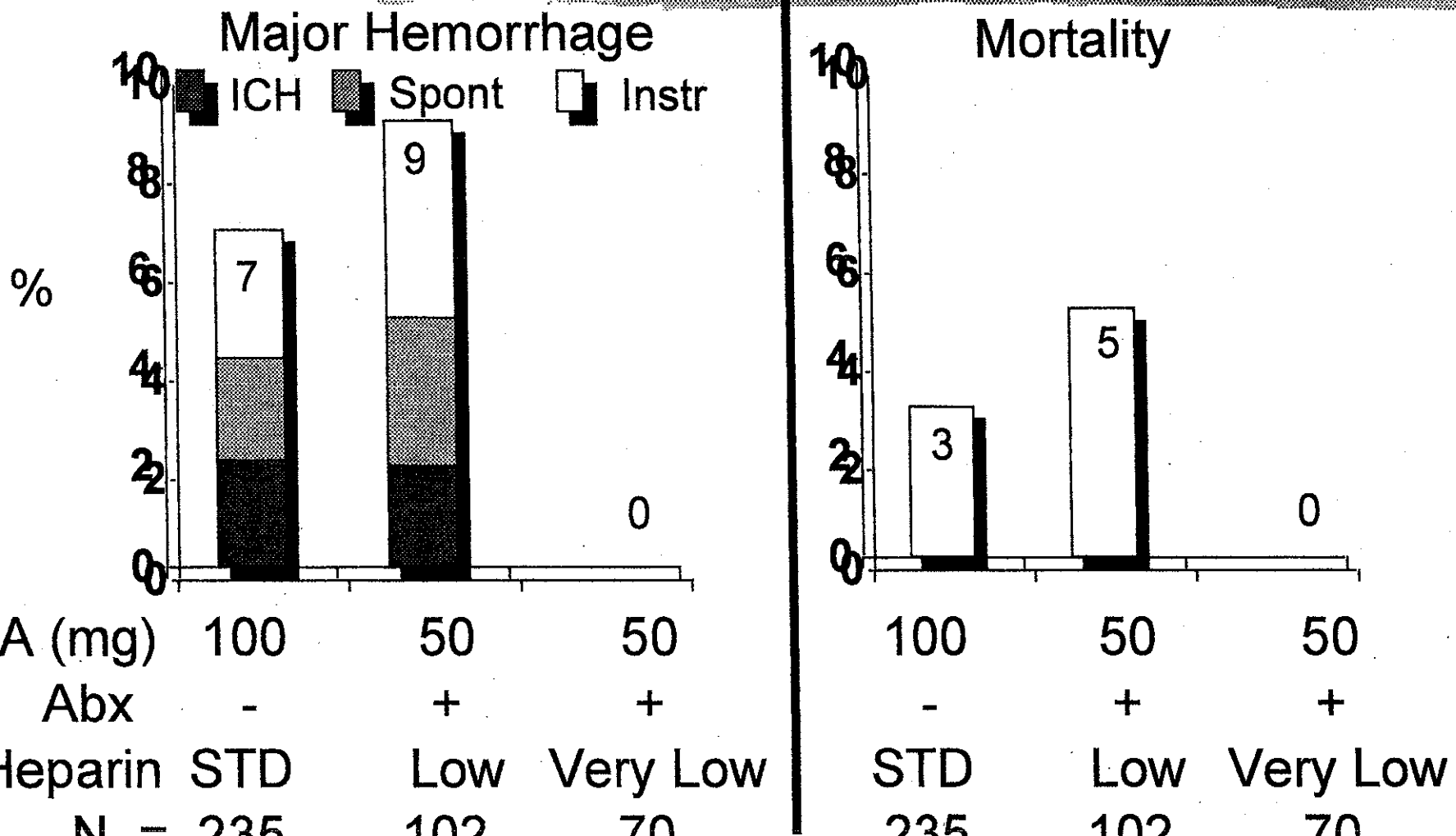
TIMI 3 FLOW AT 90 MINUTES FOLLOWING 60 MINUTES OF tPA



*(bolus 15 mg, inf 35 mg x 60 m)

Safety Experience to Date

Dose Finding and Confirmation



POSSIBLE PHASE III STRATEGIES

- More aggressive opening of arteries
  - Combination may open more arteries
- Safer opening of arteries
  - Less bleeding with reduced heparin and lytic doses
  - Less reocclusion?
  - Better microvascular flow?
- Difficult to assess ultimate tradeoff with surrogates

Conclusions

- *Angiographic surrogate in Phase II*
  - *Allows small n for dose screening/selection*
  - *Does not capture full 'net effect' of treatment (may be wrong surrogate to select a regimen!)*
  - *Not a substitute for Phase III*
- *Other surrogates are also used*
  - *Bleeding is most commonly used*
  - *Better combination of multiple surrogates may be helpful*